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EXAMINER
BAUM, STUART F

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 07/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/934,066	GRUIS ET AL.	
	Examin r	Art Unit	
	Stuart F. Baum	1638	

-- The MAILING DATE of this communicati n appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 4/28/2003 .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-37 is/are pending in the application.

4a) Of the above claim(s) 13-37 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-12 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachm nt(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 8 7
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

1. Claims 1-37 are pending.

2. Applicant's election without traverse of Group I, claims 1-12, including the nucleic acid sequence of SEQ ID NO:1 encoding the amino acid sequence of SEQ ID NO:2 in Paper No. 6 is acknowledged.

Claims 13-37 have been withdrawn from consideration because the claims are drawn to non-elected inventions.

3. Claims 1-12 are examined in the present office action.

Specification

4. On page 35, line 21, "two" is misspelled.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection includes dependent claims.

In claim 1, the metes and bounds of "genetically modified" have not been defined. It is unclear what types of genetic modification are encompassed in Applicants' claim.

In claim 1, the recitation "protein storage tissue" has not been defined. Applicant has not specified what delineates a protein storage tissue from a non-storage tissue. In addition, in some plants, proteins are stored in one type of organ whereas in other plants that organ may not be considered as a "protein storage tissue", e.g., the modified leaves of bulbs compared to leaves of a plant like corn.

In claim 2, Applicant has specified that the "protein storage tissue is seed". A seed is not a tissue. It is suggested to amend the claim to recite "protein storage tissue located within a seed".

In claim 3, tubers, roots and leaves are not tissues, but rather, they are classified as plant organs made up of different tissues.

In claim 4, the metes and bounds of "vacuolar processing enzymes" have not been defined. Applicant has not explicitly stated what enzymes are considered to be "vacuolar processing enzymes".

In claim 6, the metes and bounds of "sequence variant" have not been defined. It is not clear what constitutes a "sequence variant" and when is a sequence not considered a "sequence variant".

In claims 6, the recitation "protease activity" has not been defined. Applicants have not specified what constitutes "protease activity" and how one would assay for such activity.

In claim 6, the metes and bounds of "stringent conditions" have not been defined. Applicant has not explicitly stated in the specification the conditions and reagents required to achieve "stringent hybridization conditions". All subsequent recitations of "stringent conditions" are also rejected.

In claim 11, it is unclear if "transformed" refers to presence of original transgene, or presence of any newly-introduced transgene, such as antibiotic resistance gene that was introduced into a seed which has lost the original transgene due to meiotic segregation. Amending the claim to recite that the seeds comprise the construct that was originally introduced into the parent seed would overcome the rejection.

In claim 12, 2nd line, a polypeptide is not operably linked to a promoter, because a polypeptide comprises amino acids and not nucleotide base pairs as is the composition of the promoter. It is suggested to amend the claim to recite "a promoter operably linked to a nucleic acid encoding a polypeptide of interest".

1st Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Applicants claim a plant that is genetically modified to reduce the activity of one or more proteases in a tissue, or wherein said plant is transformed with an expression cassette comprising a promoter operably linked with any sequence polyuncleotide encoding any

product, including antisense RNA or any polypeptide of interest, including any mutant or inhibitor of any protease of any type from any source and of any sequence.

The Applicants do not identify structural, genotypic, or phenotypic features unique to the genetically modified plant or transformed plant, or any structural features common to the broad genus of polynucleotides used to transform the plant. The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In summary, the court stated that a written description of an invention requires a precise definition, one that defines the structural features of the chemical genus that distinguishes it from other chemical structures. A definition by function does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Since the genetic material has not been described by genotype, phenotype, specific structural features or by specific function, the specification fails to provide an adequate written description to support the generic claims.

2nd Written Description

7. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Applicants claim a plant that is genetically modified to reduce the activity of one or more proteases in a tissue, wherein different groups or types of proteases are specified in claim 4

and wherein the group of proteases is further limited to those specified in claim 5, or wherein the protease comprises a fragment containing at least 10 contiguous amino acids as set forth in SEQ ID NO:2, a sequence variant of the sequence set forth in SEQ ID NO:2 which is encoded by a nucleotide sequence that hybridizes under stringent conditions to SEQ ID NO:1, or a sequence variant having 60% sequence identity to SEQ ID NO:2 or wherein said plant is transformed with an expression cassette comprising a promoter operably linked with a polypeptide of interest (see 112 2nd rejection above).

Applicants have only disclosed the nucleic acid sequence of the *Arabidopsis* protease ε-vacuolar processing enzyme of SEQ ID NO:1 encoding SEQ ID NO:2 and have not disclosed any specific structural, physical and/or chemical properties for the claimed sequence. Applicants have claimed an assortment of proteases in claims 4 and 5 but Applicants have not disclosed any identifying characteristics, structural or sequence information that one skilled in the art could use to identity the claimed species. In addition, Applicants have not presented a description of domains that are specific to the ε-vacuolar processing enzyme of SEQ ID NO:1, nor domains that are important for its proper function. Given the lack of description, one skilled in the art would not be able to identify sequences with less than 100% sequence identity that still maintained the proper activity. The claims recite sequence variants whose nucleic acid sequences hybridize to SEQ ID NO:1 and sequences exhibiting 60% sequence identity to SEQ ID NO:1 but Applicants have not disclosed a representative number of species as encompassed by the claims. The claims encompass mutants and allelic variants and thus imply that structural variants exist in nature, yet no structural variant has been disclosed. The implication is that there is a gene and a protein other than that disclosed which exists in nature, but the structure thereof is

not known. Thus, there are insufficient relevant identifying characteristics to allow one skilled in the art to predictably determine such mutants and allelic variants from other plants and organisms, absent further guidance. Therefore, the written description requirement is not satisfied. Therefore, one skilled in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention. (see Written Description Requirement published in Federal Register/Vol.66, No. 4/ Friday, January 5, 2001/Notices; p. 1099-1111).

Scope of Enablement

8. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *Arabidopsis* plants in which the nucleic acid molecule of SEQ ID NO:1 encoding the ε-vacuolar processing enzyme (ε-VPE) of SEQ ID NO:2 is mutant (page 34, line 12 to page 35, line 22) does not reasonably provide enablement for claims broadly drawn to any plant that is genetically modified to reduce or eliminate the activity of any protease wherein the protease is expressed in any tissue wherein the protease can be any of the types of proteases as listed in claims 4 and 5, or a protease comprising a fragment of the amino acid sequence set forth in SEQ ID NO:2, wherein the fragment comprises at least 10 contiguous amino acids of SEQ ID NO:2, or wherein the amino acid sequence comprises a sequence variant and is encoded by a nucleotide sequence that hybridizes under stringent conditions to SEQ ID NO:1 or wherein the sequence variant is encoded by a nucleotide sequence exhibiting 60% sequence identity to SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn as discussed on page 5 of this office action. Applicants have not reduced to practice their broadly claimed invention. Applicants have only disclosed *Arabidopsis* plants that have been transposon tagged but they have not taught or disclosed any of the other methods to reduce the activity of an enzyme, i.e, antisense technology or protease inhibitors, nor have Applicants taught how one skilled in the art would locate or verify the existence of any of the proteases that are claimed.

Applicants' claims read on methods of down-regulating protein expression using unpredictable antisense technology. Bryant (1989, Trends in Biotechnology 7(2):20-21) teaches using antisense to down-regulate chalcone synthase did not always produce plants with the desired result. It was not clear why plants were produced with all levels of regulated chalcone synthase, from plants exhibiting suppression to plants exhibiting a wild-type phenotype (page 20, right column, 1st paragraph). Bryant suggests that "position effect" influences transgene expression (page 20, right column, 2nd paragraph). Martienssen (1998, PNAS 95:2021-2026) teaches essential genes cannot be down-regulated because suppression would lead to dominant lethal phenotypes that cannot be maintained (page 2021, left column, 2nd paragraph).

Applicants' claims are drawn to proteases comprising fragments of SEQ ID NO:1. The state-of-the-art teaches using sequences exhibiting below a 100% sequence identity as compared to a reference sequence produces unpredictable RNA degradation results. Moonan et al (2002, Journal of Virology 76(3):1339-1348) teach " sugarcane plants expressing untranslated viral capsid sequences of *Sorghum mosaic virus* strain SCH, challenged with SrMV viruses of strains SCM and SCI and *Sugarcane mosaic virus* strain, show various levels of virus resistance that correlated with the percentage of sequence identity of the transgenes to the sequence of the

challenging virus" (page 1347, 1st paragraph, right column). Therefore, the protection achieved using sequences that exhibited less than 100% sequence identity to the respective viral gene resulted in an inferior viral protection.

It cannot be predicted by one of skill in the art that proteases comprising a fragment of SEQ ID NO:2 will still have the same activity as SEQ ID NO:2, or have any protease activity at all. Bowie et al (1990, Science 247:1306-10) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of the protein to fold into unique three-dimensional structures that allows it to function and carry out the instructions of the genome. The cited reference also teaches that the prediction of protein structure from sequence data and, in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein, is extremely complex (pg 1306, left column). Bowie et al teach that while it is known that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or none at all (pg 1306, right column). The sensitivity of proteins to alterations in even a single amino acid in a sequence is exemplified by McConnell et al (2001, Nature 411 (6838):709-713), who teach that the replacement of a glycine residue located within the START domain of either the PHABULOSA or PHAVOLUTA protein receptor with either an alanine or aspartic acid residue, alters the sterol/lipid binding domain. This change renders the protein constitutively active and therefore creates a dominant mutation which has a drastic alteration in phenotype compared to wild-type *Arabidopsis* plants.

Given the claim breadth, unpredictability and lack of guidance as stated above; given the breadth of the claims which encompass a multitude of sequences and plants that have not been exemplified; it would require undue experimentation by one skilled in the art to identify and evaluate a multitude of non-exemplified sequences encoding a multitude of non-exemplified RNA or polypeptide products for their ability to reduce or eliminate the activity of any protease, and to verify that a specific protease has been targeted.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-3, 6-7, and 11-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Hilder et al (1987, Nature 300:160-163).

The claims are drawn to a plant that is genetically modified to reduce or eliminate the activity of one or more proteases in its protein storage tissue, wherein the protein storage tissue is located in a seed, tuber, roots, or leaves, and wherein the plant is a dicot. Claim 6 is broadly drawn to the inhibition of any protease of any sequence which is any "variant" of SEQ ID NO:2, and which is encoded by any sequence hybridizing to SEQ ID NO:1 under conditions of low stringency. Applicants also claim a seed of a plant transformed with their construct. Lastly, Applicants claim a plant transformed with an expression cassette comprising a promoter operably linked to a polypeptide of interest. Because of the 112 2nd paragraph indefiniteness of "protein storage tissue" as discussed above, the Office interprets this phrase to mean the reduction or elimination of protease activity in any tissue.

Hilder et al teach tobacco plants that have been genetically modified comprising a cowpea trypsin inhibitor which would reduce the activity of proteases. Given that Applicants used the 35S promoter (page 161, right column, last paragraph), which is a constitutive promoter expressed in all tissues, it would inherently be expressed in seeds and as such, Hilder et al, anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1, 4, and 6-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scott et al (September, 1999 U.S. Patent Number 5,955,653) taken with by Mariani et al (March, 1998, U.S. Patent Number 5,723,763).

The claims are drawn to a plant that is genetically modified to reduce or eliminate the activity of one or more proteases in its protein storage tissue, wherein the protease is a papain-type protease, and wherein the plant is either a monocot or dicot, rice or canola, respectively. Applicants also claim a seed of a plant transformed with their construct. Lastly, Applicants claim a plant transformed with an expression cassette comprising a promoter operably linked to a polypeptide of interest. Because of the 112 2nd paragraph indefiniteness of "protein storage

tissue" as discussed above, the Office interprets this phrase to mean the reduction or elimination of protease activity in any tissue.

Scott et al teach the use of a gene encoding the protease actinidin as a means of creating male-sterile plants (column 14, Example 3) including *Brassica napus* (column 16, Example 4B). Scott et al teach papain is another example of a protease that can be used in place of actinidin (column 6, lines 51-53). Scott et al also teach the use of antisense molecules to reduce or eliminate the activity of a protein in a plant (column 16, line 62 through column 17, line 4).

Scott et al does not teach or suggest making male-sterile and fertility-restored monocot plants via the inhibition of a protease.

Mariani et al disclose the importance of male-sterile and fertility-restored monocot plants, including rice, and also suggest the use of antisense RNA as a means of fertility restoration (column 7, lines 29-41; column 14, lines 40-58).

Given the recognition of those of ordinary skill in the art the value of generating male sterile plants in which the protease papain is used to induce male-sterility and the value of subsequently restoring fertility as taught by Scott et al., it would have been obvious to utilize the methods of Scott et al and to transform monocot plants, e.g., rice, to produce a rice plant that could be used for breeding as suggested by Mariani et al. It would have also been obvious to utilize the antisense method taught by Scott et al to reduce or eliminate the protease activity for fertility restoration, as suggested by Mariani et al.

Thus the claimed invention would have been *prima facie* obvious as a whole to one of ordinary skill in the art at the time it was made, especially in the absence of evidence to the contrary.

11. Entire SEQ ID NO:1 encoding SEQ ID NO:2 is free of the prior art, given the failure of the prior art to teach or reasonably suggest an isolated nucleic acid sequence of SEQ ID NO:1 encoding a polypeptide of SEQ ID NO:2. Claim 5 is deemed free of the prior art, given the failure of the prior art to teach or reasonably suggest plant transformation to inhibit any of the claimed proteases.

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stuart Baum whose telephone number is (703) 305-6997. The examiner can normally be reached on Monday-Friday 8:30AM – 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 or (703) 305-3014 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist, who may be contacted at 308-0196.

Stuart F. Baum Ph.D.

July 10, 2003

DAVID T. FOX
PRIMARY EXAMINER
GROUP ~~180~~ 1638